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PER(3,6-ANHYDRO)CYCLODEXTRIN DERIVATIVES, THEIR  
PREPARATION AND THEIR USE FOR SEPARATING IONS, IN  
PARTICULAR ANIONS BASED ON CHROMIUM AND MANGANESE

5

## DESCRIPTION

## TECHNICAL FIELD

10 The subject of the present invention is novel per(3,6-anhydro)cyclodextrin derivatives and polymers based on per(3,6-anhydro)cyclodextrins, which can be used in particular for binding and separating ions such as anions based on chromium and manganese.

15 This invention finds its application in the field of environmental decontamination in relation to these polluting ions, and for human decontamination.

## PRIOR STATE OF THE ART

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Cyclodextrins or cyclomaltooligosaccharides are compounds of natural origin formed by the cyclic linkage of  $\alpha$ -(1,4)-linked glucose units. Derivatives thereof may consist of  $\alpha$ -(1,4)-linked maltose units.

25

Numerous studies have shown that these compounds could form inclusion complexes with hydrophobic molecules, thus allowing their solubilization in aqueous media. Numerous applications have been proposed in order to  
30 exploit this phenomenon, in particular in the pharmaceutical field, as is described by D. Duchêne "Pharmaceutical application of cyclodextrins" in "Cyclodextrins and their industrial uses". D. Duchêne Ed., Editions de Santé, Paris, 1987, pages 213-257 [1].

35

Among the very many modified derivatives of these cyclodextrins, those for which the cavity is turned inside out exhibit advantageous properties even though their capacity to enclose organic molecules is lost or  
5 is very limited. Nevertheless, this capacity to enclose hydrophobic molecules can be recovered if the chain substituting the hydroxyl in C<sub>2</sub> of the cyclodextrin is longer. Compounds of this type are the per(3,6-anhydro)cyclodextrins.

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The synthesis of these peranhydrocyclodextrins has been described since 1991 in document [2]: Gadelle A. and Defaye J., *Angew. Chem. Int. Ed. Engl.*, (1991), 30, pages 78-79; and document [3]: Ashton P.R., Ellwood P.,  
15 Staton I. and Stoddart J.F., *Angew. Chem. Int. ed. Engl.*, (1991) 30, pages 80-81, and it has been shown that these derivatives have advantageous solubilities both in water and in organic solvents. Some subsequent studies (document [4]: Yamamura H. and Fujita K. *Chem.*  
20 *Pharm. Bull.*, (1991) 39, pages 2505-2508; document [5]: Yamamura H., Ezuka T., Kawase Y., Kawai M., Butsugan Y. and Fujita K., *J. Chem. Soc., Chem. Com.*, (1993), pages 636-637; and document [6]: Yamamura H. Nagaoka H., Kawai M. and Butsugan Y., *Tetrahedron Lett.* (1995) 36,  
25 pages 1093-1094) have furthermore shown that these peranhydro derivatives could complex alkali metal ions with a nonnegligible selectivity.

The document FR-A 2 744 124 [7], the document  
30 FR-A 2 764 525 [8] and the document FR-A 2 807 044 [9] mention other per(3,6-anhydro)cyclodextrin derivatives substituted at the 2-position, which are used for the separation of various ions, in particular potassium and caesium in the case of document [7] by virtue of the  
35 presence of the acetyl substituent, or lead in the case

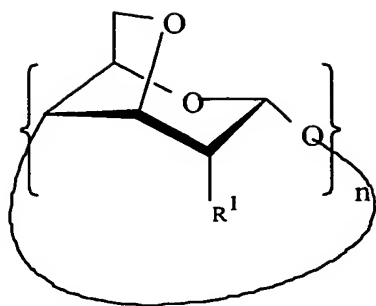
of document [8] by virtue of the presence of a methoxy  
substituent or polluting ions such as the cobalt or  
uranyl ion and the lanthanide ions in the case of  
document [9] by virtue of the presence of a substituent  
5 -O-CH<sub>2</sub>-CO<sub>2</sub>H.

Nevertheless, the derivatives described in these  
documents do not make it possible to bring about a  
satisfactory separation by complexing the anions based  
10 on chromium and manganese, which can pollute the  
environment.

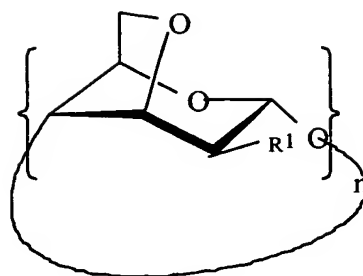
#### DISCLOSURE OF THE INVENTION

15 The subject of the present invention is precisely novel  
derivatives and novel polymers of  
peranhydrocyclodextrins in which the substituent at the  
2-position has been chosen so as to confer on these  
compounds properties of complexing anions based on  
20 chromium or manganese, such as the chromate, bichromate  
and permanganate anion.

According to the invention, the per(3,6-  
anhydro)cyclodextrin derivative corresponds to one of  
25 the following formulae (I) or (II):



(I)



(II)

in which:

- 5 - at least one of the groups  $R^1$  represents a group  $-OCONHR^2$  and the other groups  $R^1$ , which may be identical or different, represent a group corresponding to one of the formulae:  $-OCONHR^2$ ,  $-OH$ ,  $-OR^3$ ,  $-SH$ ,  $-SR^3$ ,  $-OCOR^3$ ,  $-NH_2$ ,  $-NHR^3$ ,  $-NR^3R^4$ ,  $-CONH_2$ ,  $-CONHR^3$ ,  $-CONR^3R^4$ ,  $-CN$ ,  $-COOR^3$ ,  $-OCH_2CO_2H$ ,  $-COOH$  and  $-R^3$ , in which the group(s)  $R^2$ , which are identical or different, represent a saturated or unsaturated aliphatic group,  $R^3$  and  $R^4$ , which are identical or different, represent a saturated or unsaturated, aliphatic or aromatic hydrocarbon group optionally substituted with halogen atoms which may contain one or more heteroatoms chosen from O, S and N, and/or
- 10
- 15
- 20 - at least one of the groups  $R^1$  represents a group  $-OCONH(CR^5R^6)_mNHCOOR^7$ , the other groups  $R^1$  corresponding to the same definition as that given above,  $R^5$  and  $R^6$ , which are identical or different, represent H or a saturated or unsaturated aliphatic group, and  $R^7$  represents a glucosidic or
- 25

maltosidic unit of the peranhydrocyclodextrin and m is an integer ranging from 1 to 20;

- n is equal to 6, 7 or 8.

5

In the cyclodextrin derivative of formula (I) or (II), the aliphatic or aromatic hydrocarbon groups capable of being used for  $R^3$  and  $R^4$  may be of various types. They consist of a hydrocarbon chain in which some carbon  
10 atoms may be replaced with one or more heteroatoms such as O, S and N, and they may contain one or more ethylenic or acetylenic unsaturations. Moreover, the hydrocarbon group may be substituted with halogen atoms. When  $R^3$  and  $R^4$  are aliphatic hydrocarbon groups,  
15 they may in particular represent a linear or branched alkyl group of 1 to 20 carbon atoms, such as a methyl, ethyl, n-propyl or i-propyl group. When  $R^3$  and  $R^4$  are aromatic hydrocarbon groups, they may in particular represent the phenyl group or the tosyl group,  
20 optionally substituted, for example, with alkyl groups of 1 to 20 carbon atoms.

In the peranhydrocyclodextrin derivative of formula (I) or (II), when at least one of the groups  $R^1$  represents  
25 the group  $-\text{OCONHR}^2$ , the group(s)  $R^2$ , which are identical or different, (the groups  $R^2$  when several groups  $R^1$  represent  $\text{OCONHR}^2$ ), represent a saturated or unsaturated aliphatic chain, that is to say an alicyclic chain which may optionally contain  
30 unsaturations. In particular, the group(s)  $R^2$  may represent a linear or branched alkyl group comprising from 1 to 10 carbon atoms, such as a methyl, ethyl or hexyl group.

In the peranhydrocyclodextrin derivative of formula (I) or (II), when at least one of the groups  $R^1$  represents the group  $-OCONH(CR^5R^6)_mNHCOOR^7$ , the groups  $R^5$  and  $R^6$ , which are identical or different, represent H or a saturated or unsaturated aliphatic group, that is to say an alicyclic chain which may optionally contain unsaturations. In particular, the groups  $R^5$  and  $R^6$  may represent a linear or branched alkyl group containing from 1 to 10 carbon atoms, such as a methyl or ethyl group. In accordance with the invention, the group  $-OCONH(CR^5R^6)_mNHCOOR^7$  serves to join two glucosidic units (if the cyclodextrin corresponds to formula (I)) or maltosidic units (if the cyclodextrin corresponds to formula (II)) of a same peranhydrocyclodextrin derivative,  $R^7$  thus corresponding to a glucosidic or maltosidic unit of the same peranhydrocyclodextrin derivative according to the invention.

According to a preferred embodiment of the invention, the per(3,6-anhydro)cyclodextrin derivative is an  $\alpha$ -cyclodextrin derivative, that is to say that, in formulae (I) and (II) given above,  $n$  is equal to 6.

Preferably still, the derivative used corresponds to formula (I) or (II), in which all the groups  $R^1$  represent the group  $-OCONHR^2$  with  $R^2$  having the meaning given above, and  $n$  is equal to 6. In particular, all the groups  $R^2$  may represent an ethyl or hexyl radical.

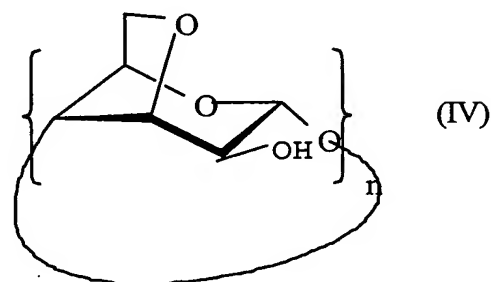
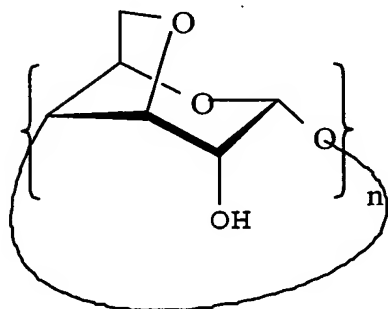
Generally, the cyclodextrin derivatives of the invention may be prepared in the following manner.

When the cyclodextrin derivative corresponds to formula (I) or (II) given above, in which at least one of the groups  $R^1$  represents the group  $-O-CO-NHR^2$  and/or

-OCONH(CR<sup>5</sup>R<sup>6</sup>)<sub>m</sub>NHCOOR<sup>7</sup>, the other possible groups R<sup>1</sup> representing a group such as those proposed above and n being equal to 6, 7 or 8, and m is an integer ranging from 1 to 20, it may be prepared by a method comprising

5 successively:

- a step consisting in reacting a per(3,6-anhydro)cyclodextrin corresponding to one of the following formulae (III) or (IV):



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in which n is equal to 6, 7 or 8, with an isocyanate of formula OCN-R<sup>2</sup> and/or a diisocyanate OCN(CR<sup>5</sup>R<sup>6</sup>)<sub>m</sub>NCO in a quantity such that at least one of the OH groups represented on formulae (III) or (IV) is converted to a

15 group -OCONHR<sup>2</sup> and/or to a group -OCONH(CR<sup>5</sup>R<sup>6</sup>)<sub>m</sub>NHCOOR<sup>7</sup>; and

- a step consisting, when not all the OH groups have been converted to a group -OCONHR<sup>2</sup> and/or -OCONH(CR<sup>5</sup>R<sup>6</sup>)<sub>m</sub>NHCOOR<sup>7</sup>, in optionally reacting the remaining -OH groups with one or more reagents in order to convert them to the desired groups R<sup>1</sup> different from -OCONHR<sup>2</sup> and/or -OCONH(CR<sup>5</sup>R<sup>6</sup>)<sub>m</sub>NHCOOR<sup>7</sup>.
- 20

When the cyclodextrin derivative corresponds to formula (I) or (II) given above, in which the other groups  $R^1$  represent  $-OR^3$  with  $R^3$  having the meaning given above, the procedure is carried out by reacting the partially modified cyclodextrin, obtained after the first step mentioned above, with an alkali metal hydride in order to convert the  $-OH$  group(s) to  $OM$  groups with  $M$  representing an alkali metal and then the derivative obtained is reacted with a halide of formula  $R^3X$  in which  $R^3$  has the meaning given above and  $X$  is a good leaving group such as a halogen atom.

When the cyclodextrin derivative corresponds to formula (I) or (II) given above, in which the other groups  $R^1$  represent  $-OCOR^3$ , the procedure is carried out, in a first step, as above (i.e reaction of the partially modified cyclodextrine with an alkali metal hydride), and the derivative obtained is then reacted with an acid halide or anhydride of formula  $R^3COX$  or  $(R^3CO)_2O$  in which  $R^3$  has the meaning given above and  $X$  represent a leaving group.

When the cyclodextrin derivative corresponds to formula (I) or (II) given above, in which the other groups  $R^1$  represent  $-O-CH_2-CO_2H$ , the procedure is carried out, in a first step, as above, (i.e reaction of the partially modified cyclodextrine with an alkali metal hydride) and the derivative obtained is then reacted with a halide of formula  $X-CH_2-CO_2R_8$ , in order to obtain a group  $-O-CH_2-CO_2R_8$ , in which  $X$  represents a halogen atom and  $R_8$  represents  $H$ ,  $Si(CH_3)_3$  or an alkali metal. The peranhydrocyclodextrin derivative obtained is then optionally treated (when  $R^8$  is different from  $H$ ) with an alcohol, a slightly acidic medium or water in order



to convert the groups  $-O-CH_2-CO_2-R_8$  to a group  $-O-CH_2-CO_2H$ .

When it is desired to prepare a cyclodextrin derivative  
5 in which the other group(s)  $R^1$  represent a group of  
formula  $-SH$ ,  $-SR^3$ ,  $-NH_2$ ,  $-NHR^3$ ,  $-NR^3R^4$ ,  $-CONR^3R^4$ ,  $-CONHR^3$ ,  
 $-CONH_2$ ,  $-CN$ ,  $-COOR^3$ ,  $-COOH$ , or  $-R^3$ , with  $R^3$  and  $R^4$  having  
the meanings given above, and  $n$  is equal to 6, 7 or 8,  
it is possible to carry out the following steps by  
10 starting with a partially modified  
peranhydrocyclodextrin, that is to say in which at  
least one of the groups  $R^1$  represents  $-OCONHR^2$  and/or  
 $-OCONH(CR^5R^6)_mNHCOOR^7$  and the other groups  $R^1$  represent  
 $-OH$ , and by carrying out the following steps:

15

1) reacting this peranhydrocyclodextrin with an  
alkali metal hydride in order to convert the  $-OH$   
group(s) to  $-OM$  group(s) with  $M$  representing an  
alkali metal;

20

2) reacting the modified peranhydrocyclodextrin  
obtained in 1) with a chloride of formula  $ClSO_2R^3$   
with  $R^3$  having the meaning given above, in order  
to obtain the derivative of formula (I) or (II) in  
25 which at least one of the groups  $R^1$  is a group of  
formula  $-OSO_2R^3$ ; and

25

3) reacting the derivative obtained in the second  
step with one or more reagents appropriate for  
30 replacing  $-OSO_2R^3$  with the desired group  $R^1$ .

30

In this method, the partially modified per(3,6-  
anhydro)cyclodextrin is first of all converted to an  
alcoholate by the action of an alkali metal hydride,  
35 and then this alcoholate is converted to a derivative

containing a leaving group of formula  $-\text{OSO}_2\text{R}^3$ , which is then reacted in one or more steps with one or more reagents appropriate for replacing this leaving group with the desired group  $\text{R}^1$ .

5

Thus, in the case where  $\text{R}^1$  must represent  $-\text{NH}_2$ , it is possible to react  $\text{N}_3\text{M}$  with the compound defined in 2). The compound thus obtained, called azide, can undergo a catalytic hydrogenation or can be treated in the presence of ammonia  $\text{NH}_3$ , in order to obtain the product where  $\text{R}^1$  must represent  $-\text{NH}_2$ .

10

The product where  $\text{R}^1$  must represent  $-\text{NHR}^3$  or  $-\text{NR}^3\text{R}^4$  is obtained by reacting the compound defined in 2) with the compound  $\text{NH}_2\text{R}^3$  or  $\text{NHR}^3\text{R}^4$ .

15

In the case where  $\text{R}^1$  must represent  $-\text{SH}$  or  $-\text{SR}^3$ , it is possible to react the compound defined in 2) with a halide  $\text{X}^-$ , which gives the compound with ( $\text{R}^1 = \text{X}$ ), which is then reacted with  $\text{HS}^-$  or  $\text{R}^3\text{S}^-$  in order to give a compound where  $\text{R}^1$  will represent  $\text{SH}$  or  $\text{SR}^3$ .

20

When  $\text{R}^1$  must represent a hydrocarbon group  $-\text{R}^3$ , a reaction with  $\text{R}_2^3\text{LiCu}$  is caused to occur in order to give a final compound where  $\text{R}^3$  then represents a hydrocarbon group, as defined above.

25

Likewise, the compound where  $\text{R}^1$  represents a halogen resulting from the reaction of the compound obtained in 2) with a halide  $\text{X}^-$  can react with  $\text{CN}^-$  in order to give a final compound where  $\text{R}^1$  will represent  $-\text{CN}$ .

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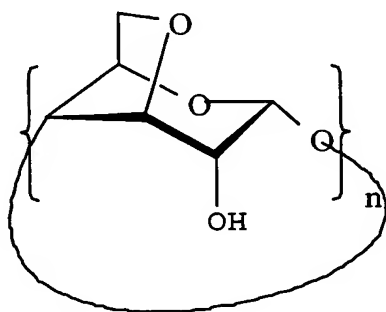
Likewise, the compound where  $\text{R}^1$  represents  $-\text{CN}$  can, by controlled hydrolysis, give a compound where  $\text{R}^1$  will represent  $-\text{CONH}_2$ . The compound where  $\text{R}^1$  represents  $-\text{CN}$

can, by complete hydrolysis, give a compound where  $R^1$  will represent  $-\text{COOH}$ .

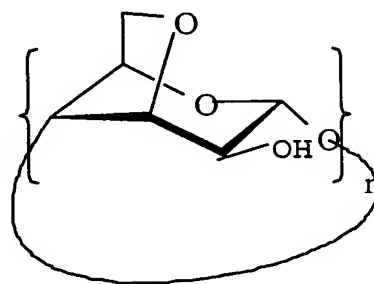
The compound where  $R^1$  represents  $-\text{COOH}$  can, by  
 5 esterification, with a compound  $R^3\text{OH}$  give a compound  
 where  $R^1$  will represent  $-\text{COOR}^3$ .

The compound where  $R^1$  represents  $-\text{COOH}$  can react with  
 $-\text{NHR}^3\text{R}^4$  or  $\text{NH}_2\text{R}^3$  in the presence of DCC  
 10 (dicyclohexylcarbodiimide) to give a compound where  $R^1$   
 will represent  $-\text{CONR}^3\text{R}^4$  or  $-\text{CONHR}^3$ .

The subject of the present invention is also a polymer  
 obtained by reacting at least two per(3,6-  
 15 anhydro)cyclodextrins of the following formulae (III)  
 or (IV):



(III)



(IV)

and a diisocyanate of formula  $\text{OCN}-(\text{CR}^5\text{R}^6)_m-\text{NCO}$ , in  
 which  $R^5$  and  $R^6$ , which are identical or different,  
 20 represent H or a saturated or unsaturated aliphatic  
 group, the OH groups having not reacted during the  
 reaction to be optionally converted into groups, which  
 are identical or different, representing groups chosen  
 from:  $-\text{OCONHR}^2$ ,  $-\text{OR}^3$ ,  $-\text{SH}$ ,  $-\text{SR}^3$ ,  $-\text{OCOR}^3$ ,  $-\text{NH}_2$ ,  $-\text{NHR}^3$ , -

$\text{NR}^3\text{R}^4$ ,  $-\text{CONH}_2$ ,  $-\text{CONHR}^3$ ,  $-\text{CONR}^3\text{R}^4$ ,  $-\text{CN}$ ,  $-\text{COOR}^3$ ,  $-\text{OCH}_2\text{COOH}$ ,  $-\text{COOH}$  and  $-\text{R}^3$ , in which the group(s)  $\text{R}^2$  represent a saturated or unsaturated aliphatic group,  $\text{R}^3$  and  $\text{R}^4$ , which may be identical or different, represent a  
5 saturated or unsaturated, aliphatic or aromatic hydrocarbon group optionally substituted with halogen atoms which may contain one or more heteroatoms chosen from O, S and N, and n is equal to 6, 7 or 8 and m is an integer ranging from 1 to 20.

10

In this polymer, at least two per(3,6-anhydro)cyclodextrin derivatives are linked by at least one carbamate bond of the  $-\text{O}-\text{CO}-\text{NH}(\text{CR}^5\text{R}^6)_m\text{NH}-\text{CO}-\text{O}-$  type, this bond being formed by reaction of two  $-\text{OH}$  groups at  
15 the 2-position of a glucosidic entity or maltosidic entity of two per(3,6-anhydro)cyclodextrins. This polymer may also contain  $-\text{O}-\text{CO}-\text{NH}(\text{CR}^5\text{R}^6)_m\text{NH}-\text{CO}-\text{O}-$  bonds formed by reaction of the diisocyanate mentioned above with two  $-\text{OH}$  groups of two glucosidic units or  
20 maltosidic units of the same peranhydrocyclodextrin. Finally, this polymer may also comprise  $-\text{O}-\text{CO}-\text{NH}(\text{CR}^5\text{R}^6)_m\text{N}=\text{C}=\text{O}$  bonds, one end having reacted with an  $-\text{OH}$  of a cyclodextrin unit, the other end not having reacted.

25 In this polymer, the groups  $\text{R}^5$  and  $\text{R}^6$ , which are identical or different, may represent hydrogen or a saturated or unsaturated aliphatic group.

In particular, the groups  $\text{R}^5$  and  $\text{R}^6$  may represent a  
30 linear or branched alkyl group containing from 1 to 10 carbon atoms, such as a methyl or ethyl group.

In this polymer, the aliphatic or aromatic hydrocarbon groups which can be used for  $\text{R}^3$  and  $\text{R}^4$  may be of various  
35 types. They consist of a hydrocarbon chain in which

some carbon atoms may be replaced with one or more heteroatoms such as O, S and N and they may contain one or more unsaturations, for example ethylenic or acetylenic unsaturations. Moreover, the hydrocarbon  
5 group may be substituted with halogen atoms. When  $R^3$  and  $R^4$  are aliphatic hydrocarbon groups, they may in particular represent a linear or branched alkyl group of 1 to 20 carbon atoms. When  $R^3$  and  $R^4$  are aromatic hydrocarbon groups, they may in particular represent  
10 the phenyl group or the tosyl group, optionally substituted, for example, with alkyl groups of 1 to 20 carbon atoms.

In this polymer, when at least one of the groups  $R^1$   
15 represents the group  $-\text{OCONHR}^2$ , the group(s)  $R^2$  represents a saturated or unsaturated aliphatic chain. In particular,  $R^2$  may represent a linear or branched alkyl group comprising from 1 to 10 carbon atoms, such as a methyl, ethyl or hexyl group.

20 In the same manner as for the compounds of formula (I) and (II), the cyclodextrin units linked in the polymer described above comprise at least, partially, at the 2-positions of the anhydroglucose rings (if the polymer  
25 is obtained from the cyclodextrins of formula (III)) or anhydromaltose rings (if the polymer is obtained from the cyclodextrins of formula (IV)), bonds of the carbamate type.

30 Preferably, the subscript  $n$  in this polymer is equal to 6 and  $R^5$  and  $R^6$  both represent H and  $m$  is equal to 6.

Preferably still, in this polymer, all the  $-\text{OH}$  groups  
35 react with the diisocyanate mentioned above to give a carbamate bond.

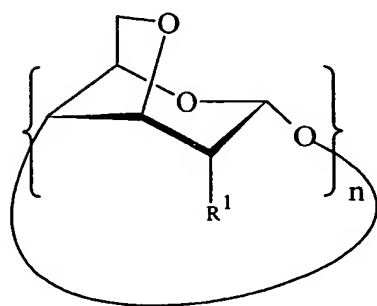
The applicant has discovered, surprisingly, that, by virtue of the presence at the 2-position of groups comprising at least one carbamate functional group

5  $\text{—O—}\overset{\text{O}}{\parallel}\text{C—NH—}$ , the per(3,6-anhydro)cyclodextrin derivatives described above and the per(3,6-anhydro)cyclodextrin polymers may be used in particular for the binding and separation of ions, more particularly of anions based on chromium and/or  
10 manganese.

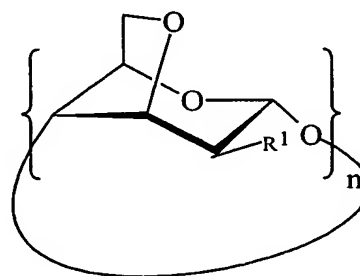
Accordingly, the subject of the invention is also a method for binding and separating ions, comprising the steps consisting in:

15 - bringing a medium containing the said ions into contact with:

1) a per(3,6-anhydro)cyclodextrin derivative corresponding to one of the following formulae (I) or (II):  
20



(I)



(II)

in which:

- 5       - at least one of the groups  $R^1$  represents a group -  
OCONHR<sup>2</sup> and the other groups  $R^1$ , which may be  
identical or different, represent a group  
corresponding to one of the formulae: -OCONHR<sup>2</sup>, -  
OH, -OR<sup>3</sup>, -SH, -SR<sup>3</sup>, -OCOR<sup>3</sup>, -NH<sub>2</sub>, -NHR<sup>3</sup>, -NR<sup>3</sup>R<sup>4</sup>, -  
CONH<sub>2</sub>, -CONHR<sup>3</sup>, -CONR<sup>3</sup>R<sup>4</sup>, -CN, -COOR<sup>3</sup>, -OCH<sub>2</sub>CO<sub>2</sub>H, -  
10       COOH and -R<sup>3</sup>, in which the group(s)  $R^2$ , which are  
identical or different, represent a saturated or  
unsaturated aliphatic group,  $R^3$  and  $R^4$ , which are  
identical or different, represent a saturated or  
unsaturated, aliphatic or aromatic hydrocarbon  
15       group optionally substituted with halogen atoms  
which may contain one or more heteroatoms chosen  
from O, S and N, and/or
- 20       - at least one of the groups  $R^1$  represents a group -  
OCONH(CR<sup>5</sup>R<sup>6</sup>)<sub>m</sub>NHCOOR<sup>7</sup>, the other groups  $R^1$   
corresponding to the same definition as that given  
above,  $R^5$  and  $R^6$ , which are identical or different,  
represent H or a saturated or unsaturated aliphatic  
group, and  $R^7$  represents a glucosidic or maltosidic  
25       unit of the peranhydrocyclodextrin and m is an  
integer ranging from 1 to 20;
- n is equal to 6, 7 or 8,  
and/or
- 30    2) a polymer obtained by reacting at least two  
per(3,6-anhydro)cyclodextrins of formula (III) or  
(IV), as mentioned above, and a diisocyanate of  
formula OCN- (CR<sup>5</sup>R<sup>6</sup>)<sub>m</sub>-NCO, for which  $R^5$  and  $R^6$ ,  
which are identical or different, represent H or a  
35       saturated or unsaturated aliphatic group, the OH

- groups having not reacted during the reaction to be optionally converted into groups, which are identical or different, representing groups chosen from:  $-\text{OCONHR}^2$ ,  $-\text{OR}^3$ ,  $-\text{SH}$ ,  $-\text{SR}^3$ ,  $-\text{OCOR}^3$ ,  $-\text{NH}_2$ ,  $-\text{NHR}^3$ ,  $-\text{NR}^3\text{R}^4$ ,  $-\text{CONH}_2$ ,  $-\text{CONHR}^3$ ,  $-\text{CONR}^3\text{R}^4$ ,  $-\text{CN}$ ,  $-\text{COOR}^3$ ,  $-\text{OCH}_2\text{CO}_2\text{H}$ ,  $-\text{COOH}$  and  $-\text{R}^3$ , in which the group(s)  $\text{R}^2$  represents a saturated or unsaturated aliphatic group,  $\text{R}^3$  and  $\text{R}^4$ , which may be identical or different, represent a saturated or unsaturated, aliphatic or aromatic hydrocarbon group which may contain one or more heteroatoms chosen from O, S and N, and n is equal to 6, 7 or 8 and m is an integer ranging from 1 to 20, in order to bind the said ions in the form of a complex with the per(3,6-anhydro)cyclodextrin derivative or the polymer; and
- separating the said ions thus complexed from the said medium.
- The ions which can be bound or separated by the method of the invention may be of various types, such as the ions of polluting metals.

However, the method of the invention applies in particular to the binding of anions based on chromium, in particular the anions containing chromium having a valency VI such as chromate or bichromate ions, and the anions based on manganese such as the permanganate ions in the form of a complex with the per(3,6-anhydro)cyclodextrin derivative or polymers mentioned above.

Indeed, toxicological studies have made it possible to demonstrate that chromium salts having a valency VI, such as the chromate ions  $\text{CrO}_4^{2-}$  or the bichromate ions



$\text{Cr}_2\text{O}_7^{2-}$ , exhibit a very high toxicity to humans and to animals.

5 Thus, chromic acid  $\text{H}_2\text{CrO}_4$  and its salts, which are soluble in particular in the gastric juice, can cause dermatoses and ulcerations in individuals handling them.

10 Potassium dichromate can prove deadly at doses of 0.25 to 0.30 g and can cause gastric disorders and enteritis.

Chromate or bichromate ions are also found to be methaemoglobinizing poisons.

15 According to the invention, it has been found that the cyclodextrin derivatives and the per(3,6-anhydro)cyclodextrin polymers, the said cyclodextrin corresponding to the formulae (I) and (II) given above, 20 exhibit a high specificity for anions based on chromium or manganese because they exhibit for these metals a complexation capacity with very high yields.

In particular, a per(3,6-anhydro)cyclodextrin 25 derivative corresponding to formula (I), which is effective for carrying out this method, is the derivative for which all the groups  $\text{R}^1$  represent  $\text{OCONHR}^2$ ,  $\text{R}^2$  having the same definition as that given above and  $n$  is equal to 6. More precisely,  $\text{R}^2$  may 30 represent a hexyl or ethyl radical.

A polymer in accordance with the present invention, which may be effectively used in the context of the binding method, is a polymer for which  $n$  is equal to 6, 35  $\text{R}^5$  and  $\text{R}^6$  both represent H and  $m$  is equal to 6.

By virtue of these compounds, it is possible to separate the anions based on chromium and manganese from the surrounding medium in the form of a complex.

5 Accordingly, the subject of the invention is also the complexes of an ion chosen from  $\text{CrO}_4^{2-}$ ,  $\text{Cr}_2\text{O}_7^{2-}$  and  $\text{MnO}_4^-$  with a per(3,6-anhydro)cyclodextrin derivative of formula (I) or (II) described above and/or with a polymer as defined above.

10

Preferably, the complex of an ion chosen from  $\text{CrO}_4^{2-}$ ,  $\text{Cr}_2\text{O}_7^{2-}$  and  $\text{MnO}_4^-$ , when the peranhydrocyclodextrin derivative corresponds to formula (I), is such that all the groups  $\text{R}^1$  represent the group  $-\text{O}-\text{CO}-\text{NHR}^2$  and  $n$  is  
15 equal to 6,  $\text{R}^2$  having the same definition as that given above.

To carry out the method of separating ions of the invention, it is possible to use the per(3,6-anhydro)cyclodextrin derivative of formula (I) or (II)  
20 or the per(3,6-anhydro)cyclodextrin and diisocyanate polymers described above in the form of an aqueous solution or an organic solution.

25 When the medium containing the ions to be separated or to be bound is an aqueous solution, it is possible to dissolve the cyclodextrin derivative in an organic solvent which is immiscible with the aqueous solution in order to form the complex in the organic solution  
30 and to easily separate it from the aqueous solution, for example by mere decantation followed by separation of the aqueous solution and of the immiscible organic solvent containing the complexed ions.

It is also possible to use the cyclodextrin derivative or the polymers in aqueous solution, in particular to bring about decontamination of human beings or alternatively as a preparation in dressings (agarose  
5 gels).

Indeed, these compounds are biocompatible and can therefore be administered to humans and to animals to bring about the binding of chromium and manganese in the form of a complex and to thereby avoid their  
10 interaction with the organs of the human or animal body.

Accordingly, the subject of the invention is also a pharmaceutical composition for the decontamination, in  
15 relation to chromium and to manganese, of a human being, characterized in that it comprises a per(3,6-anhydro)cyclodextrin derivative corresponding to one of formulae (I) and (II) defined above and/or a per(3,6-anhydro)cyclodextrin and diisocyanate polymer as  
20 described above.

Preferably, the derivative used in this composition is such that all the groups  $R^1$  represent the group  $-O-CO-NHR^2$  and  $n$  is equal to 6,  $R^2$  having the same  
25 definition as that given above.

This composition may be administered by the oral route or by injection. Administered by the oral route, it should be packaged in a suitable manner so as to go  
30 through the stomach without being hydrolyzed.

Other characteristics and advantages of the invention will appear more clearly on reading the examples which follow, which are given by way of illustration and

without limitation, with reference to the accompanying drawings.

#### BRIEF DESCRIPTION OF THE FIGURES

5

Figure 1 is a schematic representation of the retardation factors  $R_f$  of various anions, with the per(3,6-anhydro)cyclodextrin of Example 1.

10 Figure 2 is a schematic representation of the retardation factors  $R_f$  of various cations, with the per(3,6-anhydro)cyclodextrin derivative of Example 1.

#### DETAILED DESCRIPTION OF SPECIFIC EMBODIMENTS

15

**EXAMPLE 1:** Preparation of per(3,6-anhydro)cyclomaltohexaose per-2-O-ethylcarbamate.

20 This compound corresponds to formula (I) given above in which all the groups  $R^1$  represent  $-\text{OCONHCH}_2\text{CH}_3$ .

25 1 g of per(3,6-anhydro)cyclomaltohexaose, dried under a vacuum produced by a slide vane rotary vacuum pump for 2 hours, are weighed out and there are added 50 ml of anhydrous dimethyl sulphoxide (DMSO) and 3 ml of ethyl isocyanate in the cold state. The solution is heated at 100 °C overnight. The solution is then cooled and 1.5 ml of ethyl isocyanate are added and the medium is re-heated to 100 °C.

30

After leaving overnight, the solution is cooled and then treated with 10 ml of methanol and kept stirring for 1 hour. The solution is then dried using a rotary evaporator followed by a slide vane rotary vacuum pump.

The residue obtained is then passed over a silica gel column (eluent methanol/water 1:6).

This product can be used as it is for the complexing of  
5 chromium or manganese.

**EXAMPLE 2: Preparation of per(3,6-anhydro)cyclomaltohexaose per-2-O-hexylcarbamate.**

10 This compound corresponds to formula (I) given above in which all the groups  $R^1$  correspond to  $-\text{CONH}(\text{CH}_2)_5-\text{CH}_3$  and  $n$  is equal to 6.

444 mg of per(3,6-anhydro)cyclomaltohexaose are weighed  
15 after drying for 3 hours under a slide vane rotary vacuum pump, and 25 mL of dimethyl sulphoxide (DMSO) are added under argon, followed by 1.5 mL of hexyl isocyanate. The solution is heated to 70 °C, with magnetic stirring. After heating overnight at 70 °C,  
20 the cooled solution is supplemented with 0.8 mL of hexyl isocyanate and is kept at 10 °C overnight. Next, the solution is cooled and supplemented with methanol, with stirring. After stirring for 1 hour, the solvents are removed and the residue is purified by column  
25 chromatography (silica gel, methanol/chloroform 1:6).

**EXAMPLE 3: Demonstration of the complexing of anions by the compound of Example 1, by ion-exchange plate chromatography.**

30

The use of thin layer chromatography plates charged with ions allows rapid evaluation of the complexing of these ions by the species to be evaluated; in the present case, plates of the Polygram Ionex 25-SA-Na

type (Macherey-Nagel, ref.: 80613) charged with various counterions to be evaluated.

Thus, chromatography plates are used onto which are  
5 respectively bound the ions acetyl  $\text{COO}^-$  (designated Ac in Figure 1),  $\text{PO}_4^{3-}$ ,  $\text{NO}_3^-$ ,  $\text{Cr}_2\text{O}_7^{2-}$ ,  $\text{Cl}^-$ ,  $\text{SO}_4^{2-}$ ,  $\text{HCO}_3^-$ ,  $\text{BO}_3^-$ ,  $\text{WO}_4^{2-}$ ,  $\text{MnO}_4^-$ ,  $\text{CrO}_4^{2-}$ ,  $\text{AsO}_4^{2-}$ ,  $\text{AlO}_2^-$ .

In each test, there is introduced onto the plate the  
10 compound of Example 1 which will be retained on the plate if it complexes the ions. The plates are then developed four times in water, because of the low solubility in water, and then the retardation factor  $R_f$ , which corresponds to the ratio (distance covered by  
15 the cyclodextrin derivative/distance covered by the solvent), is determined. The lower the  $R_f$ , for a given ion, the more the ion in question will form a complex with the cyclodextrin compound.

20 The results obtained are represented in Figure 1.

It is thus observed that the cyclodextrin prepared according to Example 1 has a high complexing rate for the chromium ions such as the ions  $\text{Cr}_2\text{O}_7^{2-}$  and  $\text{CrO}_4^{2-}$  and  
25 the manganese ions  $\text{MnO}_4^-$ .

Because of this, the cyclodextrin compounds according to the invention, and in particular that prepared according to Example 1, are particularly advantageous  
30 in the field of environmental contamination and in the field of human decontamination in relation to anions based on chromium and manganese.

Likewise, tests were carried out to see whether the  
35 derivatives according to the invention were capable of

complexing cations. Tests were carried out with the following ions:

Na<sup>+</sup>, K<sup>+</sup>, Cs<sup>+</sup>, NH<sub>4</sub><sup>+</sup>, Ca<sup>2+</sup>, Ba<sup>2+</sup>, Al<sup>3+</sup>, Fe<sup>3+</sup>, Co<sup>2+</sup>, Ni<sup>2+</sup>, Cu<sup>2+</sup>,  
5 Ag<sup>2+</sup>, Zn<sup>2+</sup>, Hg<sup>2+</sup>, Pb<sup>2+</sup>, La<sup>3+</sup>, Gd<sup>3+</sup>, UO<sub>2</sub><sup>2+</sup>. According to the results assembled in Figure 2, none of these cations efficiently forms a complex with the peranhydrocyclodextrin prepared according to Example 1.

10 **EXAMPLE 4:** Preparation of a polymer obtained by reacting a per(3,6-anhydro)cyclomaltohexaose and hexyl diisocyanate.

5 ml of anhydrous dimethylformamide (DMF) and 0.934 mL  
15 of hexyl diisocyanate (2 equivalents per 1 mmol of anhydro) are added to 2.5 g of per(3,6-anhydro)cyclomaltohexaose dried using a pump for 2 hours. The medium is heated to 90 °C, with stirring, and left to react overnight. The product is then  
20 supplemented with methanol (20 ml) and left to react for 1 hour. A powder is recovered by scraping, it is centrifuged and then dried. 3.21 g of polymer are recovered after air-drying at room temperature. This polymer is characterized by its microanalysis and by  
25 NMR on the solid.

**EXAMPLE 5:** Preparation of polymer complexes.

820 mg of polymer prepared in Example 4 are weighed,  
30 and a solution containing 312 mg of potassium dichromate and 10 mL of water is added thereto. The product is left overnight, with stirring. It is then centrifuged and washed with 50 mL of water and recentrifuged. The latter operation is repeated four  
35 times. The product recovered (800 mg) is analyzed by

microanalysis and NMR on the solid. It is observed that the chromium is complexed in its bichromate and chromate form. The microanalysis shows that one site out of two is occupied by the chromium and that the product is not oxidized over time.

**COMPARATIVE EXAMPLE: Preparation of complexes based on inositol.**

10 5 g of myoinositol are weighed and they are then dried using a slide vane rotary vacuum pump for 2 hours. 40 ml of dimethyl sulphoxide (DMSO) and 4.85 mL of hexyl diisocyanate are then added, with stirring. The reaction mixture is kept at 100 °C overnight. After  
15 cooling, the solution is then supplemented with 10 ml of methanol. After 1 hour, the whole is dried, precipitated from water and centrifuged.

500 mg of this polymer are then treated with an aqueous  
20 solution of potassium dichromate (500 mg, 10 mL). After leaving overnight, with stirring, at room temperature, the product is separated by decantation and taken up in water (50 mL), stirred for 1 hour and centrifuged 4 times. The residue weighed after air-drying (516 mg) is  
25 studied by NMR on the solid and sent for microanalysis. It was possible to observe that the chromium complexing rate is of the order of 8%, which is very low compared with the products of the invention. It was also possible to demonstrate that the chromium complexing  
30 the product has the valency 3. Despite the presence of residual alcohol groups, the product can be stable and can be optionally recycled.



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